REMARKS

The amendments made herein are meant to correct obvious grammatical errors and to more particularly point out the subject matter being claimed. Therefore, no new matter is raised by this amendment.

By this amendment, claim 2 is canceled and, therefore, claims 1 and 3-22 are now pending.

Reconsideration of this application is respectfully requested.

Objection to the Specification

The specification stands objected to as not being arranged properly. By this Amendment, the specification has been made to conform to the arrangement of the specification suggested by the Examiner. Therefore, it is respectfully submitted that the subject rejection has been overcome and should be withdrawn.

Rejection Under 35 U.S.C. 112, Second Paragraph

Claims 1, 4, 10, 12, and 19 stand rejected under 35 U.S.C. 112, second paragraph. By this amendment, claims 1, 4, 10, 12, and 19 have been amended to remove the language objected to by the Examiner. Accordingly, it is respectfully submitted that the subject rejection has been overcome and should be withdrawn.

Objection to the Title

The title stands rejected as being nondescriptive. By this amendment, the title has been amended to MEDICINAL AEROSOLS AND METHODS OF DELIVERY THEREOF.

Therefore, it is respectfully submitted that the subject rejection has been overcome and should be withdrawn.

Objection to the Abstract

The abstract stands rejected as not being fully commensurate in scope with the disclosure. By this amendment, the abstract has been replaced with a new abstract. It is maintained that the new abstract is commensurate in scope with the disclosure and it is respectfully submitted that the subject rejection has been overcome and should be withdrawn.

Rejection Under 35 U.S.C. 102(b)

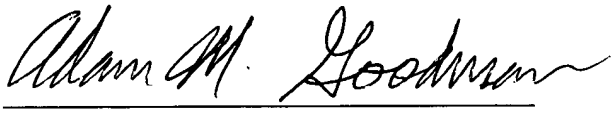
Claims 1-22 stand rejected under 35 U.S.C. 102(b) as being anticipated by Purewal, et al., U.S. Patent No. 5,225,183. The invention of claims 1-22 differ from Purewal by virtue of their requirement that the formulation be substantially free of surfactant. In fact, Purewal (column 3, lines 5-9) indicates that the presence of increased amounts of solubilised surfactant allows the preparation of stable, homogenous suspensions of drug particles and assists in obtaining stable solution formulations of certain drugs. In addition, during the litigation Re European Patent Nos. 0372,777, 0499,344, and 0553,298 before the Chancery Division (**copy attached**), an expert for 3M, the patentee, indicated that he would have understood from the statements in EP 0372,777 (the European patent corresponding with U.S. Patent No. 5,225,183) that the authors of that document had found surfactant to be a necessary component in the aerosol formulation. (See e.g. page 18). Therefore, the requirement that the formulation be substantially free of surfactant is neither disclosed nor suggested by Purewal. Accordingly, it is maintained that claims 1 and 3-22 are novel over Purewal and it is respectfully requested that the subject

rejection be withdrawn.

It is believed for the foregoing reasons that the claims warrant allowance, and such action is earnestly solicited.

Dated: August 27, 1999

Respectfully submitted,



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3RD CASE OF Level 1 printed in FULL format.

Re European Patent Nos. 0372777, 0499344 and 0553298

CHANCERY DIVISION (PATENTS COURT)

(Transcript)

HEARING-DATES: 4, 5, 6, 9, 10, 11, 12, 25, 30 JUNE 1997

30 JUNE 1997

INTRODUCTION:

This is a signed judgment handed down by the judge, with a direction that no further record or transcript need be made (RSC Ord 59, r(1) (f), Ord 68, r1). See Practice Note dated 9 July 1990, [1990] 2 All ER 1024.

COUNSEL:

S Thorley QC and H Carr for the Petitioners; D Kitchin QC and M Tappin for the Respondents

PANEL: JACOB J

JUDGMENTBY-1: JACOB J

JUDGMENT-1:

JACOB J: Norton Healthcare Ltd. ('Norton') petition for the revocation of two European patents owned by **Riker** Laboratories Inc and one owned by the Minnesota Mining and Manufacturing Company. **Riker** is a subsidiary of the latter and I shall simply call both patentees 3M. The patents were granted by the European Patent Office and are accordingly European Patents (UK). Their numbers are 0372777, 0499344 and 0553298. 344 is divided out of 777. It adds little to the case: it was agreed that I need consider just claim 5 as, in effect, a further subsidiary claim of 777. The priority date of 777 and 344 is 6 December 1988; that of 298 is 18 October 1990. 777 and 298 were each unsuccessfully opposed before the Opposition Division of the European Patent Office. Appeals are pending in each case. The Opposition Division accepted offers of amendments to 298. Formally they do not take effect until the appeal is determined. 3M therefore offer the same amendments specifically to the UK patent. It is accepted that there is no objection to the amendments and accordingly the case has proceeded on the basis of the proposed amended claims of 298.

MDIs

The patents are all for pharmaceutical formulations for the delivery of drugs by metered dose inhalers (MDIs). The inventions (if such they be) arise out of the need to find non-CFC propellants for MDIs It is therefore appropriate that I should begin with what was generally known about these by 1988. I can take it from Dr Sciarra's (3M's principal expert witness) report.

"The MDI is one of a number of devices which are (and were in the late 1980s) available for delivering drugs to the human respiratory tract. Others were single and multiple-shot dry powder inhalers ('DPIs'), nebulisers and pump spray devices . . . . MDIs consist essentially of 5 components, namely a container, a

metering, valve, the liquefied propellants with any excipients, a medicament in either suspension or solution form in the propellant system, and an adapter or mouthpiece."

I should say a little more about Dr Sciarra. He is an extremely knowledgeable man, qualified in pharmacy. He formed his own company in 1986 having spent many years in academia. He has considerable experience of aerosols (both general and MDI) He has acted as a consultant to many pharmaceutical companies in relation to their formulations

There were a number of well-known valve manufacturers Nothing turns on the detail but it was well-known that you might need some sort of lubricant within the formulation to prevent sticking Surfactants were well-known additives for this purpose. The established propellants were all CFCs and were in particular those known as P12, P11 and P114. I use here their abbreviated names rather than their full chemical names All three of these CFCs were made by chemical companies principally for other major uses. P12 was the main propellant in MDIs though its vapour pressure was a little high By adding a liquid of lower vapour pressure the resultant vapour pressure could be reduced. So P12 was generally used with some P11 or P114.

The formulations within the MDI could take the form of solutions or suspensions. In the early years of MDIs (the 1950's) solutions were favoured. One tried to dissolve the drug in the propellant. If it was not readily soluble, then a co-solvent would be used, the most common of which was ethanol (ethyl alcohol). The drug was first dissolved in water and then mixed with the co-solvent. That mixture was itself miscible with the propellant. Sometimes co-solvents were added even if the drug did dissolve in the propellant, the purpose of this being to keep the drug in solution both during preparation and during the ordinary shelf-life of the formulation - in other words for stability Ethanol was the only co-solvent which had regulatory approval.

By the late 1980's suspension formulations had evolved and were the preferred form. The drug is inherently more stable being in solid form. Here the idea is the very opposite of solutions. You want the drug particles (which are micronised in a suitable milling machine) not to dissolve. However you got another problem: agglomeration. To overcome this it was well- known to use a surfactant (which is hardly surprising). The established surfactants were three in number - sorbitan esters, oleic acid and lecithin ('the 3 surfactants'). All three were soluble in mixtures of P12/P11 or P12/P114 And all three had been proved to be non-toxic and had regulatory approval. The surfactants also coped with another problem: lubrication of the valves. Obviously valves should not only not stick but operate reliably and it was well-known to use one or other of the surfactants for lubrication purposes.

There was also a well-known problem which might arise with suspension formulations If the drug dissolved to some extent in the liquids present then you might get 'Ostwald ripening' ie. crystal growth due to fluctuations in solubility caused by temperature changes. This was but one of the things which might affect the long-term stability of a particular formulation.

I have said that suspension formulations were the preferred form. The evidence shows that a number of solution MDIs were nonetheless on the market in the late 1980's and were well- known Conveniently a lot of knowledge about MDIs which Dr Sciarra accepted was 'basic (P.442)' is summarised in a paper (I think

forming the basis of lectures) of a Mr Ranucci (D/10). Quite a lot of space in the paper is devoted to solution formulations.

It is also undisputed that a lot of work would be required with any new formulation before it could get regulatory approval. Obtaining such approval required a whole range of tests involving such things as toxicity studies with animals and long-term stability (of the formulation and the whole MDI system). The work involved would in practice take as a minimum several years, even using the known and well established surfactants (ie. the three) and, if it were used for a solution form, ethanol. This was so even using the established propellants, P12, P11 and P114 If a new formulation were to contain a new chemical (eg. solvent or surfactant) then particularly onerous regulatory testing was likely to be required. So there was every incentive to use chemicals which had regulatory approval.

Thus by the 1980's the following was common general knowledge amongst those concerned with formulating drugs for use with MDIs

(a) Both solution and suspension forms;

(b) The use of ethanol to dissolve the drug for solution forms:

(c) The use of P12 as the main propellant and P11 and/or P114 to lower vapour pressure.

(d) The use of the 3 surfactants for lubrication and anti-agglomeration in the case of suspension formulations, together with knowledge that they would dissolve in P11, which was known to be a better solvent than P12.

There was also a general (and fairly self-evident) principle which formulators went by: not to use a component at all if it was found not to be necessary, and if it was necessary, to use the minimum amount which was necessary. The art of formulation in its detailed aspects involved quite a lot of trial and error - prediction of the detailed behaviour of such things as long-term stability not being possible

The CFCs and their replacements

CFCs were originally developed in the 1930's. By the early 1970's their use was widespread for a whole variety of uses. In particular they were used as refrigerants, as blowing agents for foams, as propellants for aerosol dispensers and so on. In 1974 Molina and Rowland published a paper in Nature one of the leading scientific journals in the world) postulating that CFCs could have damaging effects on the upper atmosphere. At the time the postulate was controversial, but as time went on it became accepted as true. Pressure to abandon the use of CFCs grew In some cases this was relatively easy - and in particular in relation to general aerosols it was possible to use hydrocarbons. Bans on the use of CFCs as general aerosol propellants came into force. The ban in the US was in 1978, followed shortly by Canada, Norway and Sweden. It was estimated that some 75% of global CFC emissions came from aerosol use (70% from deodorants and hairsprays). Other major uses (particularly as refrigerants) were not banned, and there was an exemption for MDI use. It should be noted that use in MDIs formed only a very small proportion of the overall use of CFCs. This remained so even after use in general aerosols was discontinued.

It was in May 1985 that Farman, Gardiner and Shanklin of the British Antarctic Survey reported (again in Nature) the existence and growth of the ozone hole above the Antarctic. It was reported that there was a growth in chlorine in the upper atmosphere and the presence of this chlorine was attributed to the breakdown of CFCs. The chlorine would fairly self-evidently react with ozone.

Clearly something had to be done. Governments recognised this and, in a remarkable spirit of co-operation, an international treaty, called the Montreal Protocol was reached in September 1987. It was to enter force at the beginning of 1989. The Protocol set in train a machinery whereunder CFCs would be phased out. MDIs were exempted for the time being, but it was fairly obvious to their manufacturers that, even though their use was small, use in MDIs might eventually be banned. Moreover, even if the exemption continued, once the major uses were banned there was a real risk that manufacture of CFCs would stop altogether.

Thus it was in the late 1980's that MDI manufacturers knew that sooner or later they would have to turn to propellants other than CFCs. I say they knew because by that time the CFC problem was common knowledge not only throughout industry; it was also common knowledge amongst the educated public with articles appearing, for instance, in the Financial Times, the New York Times and the New Scientist. The MDI manufacturers at this time had something of a concern about a too early ban on CFCs for MDIs. The detailed work necessary to bring a new formulation to market would be substantial and take a long time. The fear was that others might not understand this; that they would assume that once a substitute propellant had become available for general use (which would mean it would have passed general toxicology tests) it could simply be used in MDIs.

Propellant manufacturers were by this time heavily engaged in the pursuit of substitutes. I have indicated that hydrocarbons had replaced CFCs for general aerosols. This had already had a major impact on some manufacturers, for instance Du Pont lost virtually all their propellant business in the late 1970's. Various manufacturers concentrated on different possible substitutes. Du Pont for instance, developed a range of dimethyl ether (DME) propellants under the name Dymel. Akzo also made DME propellants. A particular Dymel, called P22 (also made by Du Pont) contained chlorine. There was some slight concern about this also having the potential of releasing Chlorine ions in the upper atmosphere but the risk was seen as much less. Nonetheless I think it fair to say that anyone looking for a CFC substitute would prefer not to have a chlorine containing compound. This was particularly true for MDI manufacturers because the cost of a yet further change (even if well in the future) was so great: all the trials for regulatory approval would have to be gone through yet again.

One of the major manufacturers, ICI, was, by the late 1980's, particularly concentrating on a propellant called P134a. There was a mass of publicity about ICI's plans concerning this. Du Pont and one or two others also had plans for P134a. That too received publicity. Mr Thorley QC put in a chronology listing the various publicity materials concerned. Before the priority date of the first two patents I think it fair to say that anyone interested in propellants would know that ICI (and others) were planning large scale manufacture of P134a and that this propellant was seen as a substitute for the CFC P12 in general terms. You would have to be pretty blinkered not to know this by late 1988 if you were concerned with propellants. I say 'in general terms' because none of the

publicity (save for an ICI press release dated November 22nd 1988 (X 18)) mentioned possible use in MDIs or even general aerosols. The talk was basically of use as a refrigerant. However I have no doubt that any competent MDI man (or, as is accepted here, research team) would know of P 134a and that its physical properties as a propellant (ie. its boiling point) made it very close to P 12. No-one called by either side was unaware of P 134a by the priority date of the patent.

There is a dispute between the parties as to what significance a skilled MDI formulation team would have attached to P134a at this time. Norton say that by then it was the P12 replacement of choice. 3M say it was no more than one of a number of candidates and did not stand out. To this I will return, but I have said enough at this point to come to the first two patents.

Patents 777 and 344

Little turns on the detailed text of the specification (which is broadly the same for both patents) and neither side went to it much. There is no dispute of construction. The specification of 777 says:

"It has now been found that 1,1,1,2-tetrafluoroethane [i.e. P134a] has particularly suitable properties for use as a propellant for medicinal aerosol formulations for oral or nasal administration when used in combination with a surface active agent and an adjuvant having a higher polarity than P134a. (P.1, 33-36)"

It explains the use of the adjuvant thus:

"The addition of a compound of higher polarity than P134a to P134a provides a mixture in which increased amounts of surfactants may be dissolved compared to their solubility in P134a alone. The presence of increased amounts of solubilised surfactants allows the preparation of stable, homogenous suspensions of drug particles. The presence of large amounts of solubilised surfactant may also assist in obtaining stable solution formulations of certain drugs. (P.2, 13-17)"

So the adjuvant is there for dissolving surfactants. Later the specification points out it can be used to increase vapour pressure. It is elementary physics that if you mix two liquids the resultant vapour pressure is an intermediate between the two components. Normally the intermediate pressure is directly proportional to the relative quantities of the components (Raoult's law) but it was well-known that ethanol, although varying vapour pressure when added to another liquid, did not exactly obey this law.

The specification contains general information about proportions and various types of adjuvant and surfactant. But for practical purposes the adjuvant which matters is ethanol and the surfactants which matter are the 'three'. There are some examples which describe the preparation of an MDI. Most examples are for a suspension formulation. This describes the conventional 'slurry' method used in the prior art with P12 and P11 or P114. The drug and surfactant are put together, the liquid of higher boiling point (P11 in the prior art, P11 or ethanol in the patent) is added and a homogenised slurry made. This is put in a bottle and the P134a added under pressure. A valve is put on top. Examples 10-12 are for a solution formulation of a drug known as beclomethasone dipropionate

('BDP').

I can go to those claims said to have independent validity:
Claim 1

A medicinal aerosol formulation suitable for administration to a patient by oral or nasal inhalation comprising:

- a medicament, P134a, a surfactant and at least one compound having a higher polarity than P134a,

- the formulation being in the form of a solution or a suspension of medicament particles have a median particle size of less than 10 micrometres and being substantially free of P22, P32 and P143a.

I have here used the standard designations rather than full chemical names - as has everyone in this case. P22, P32 and P143a are all well-known CFCs. The adjuvant of'higher polarity' is essentially a substance which is better at dissolving things than P134a. P134a is a bad solvent and the limitation to 'higher polarity' is not much of limitation on what should be added.

The claim does not exclude the use of all CFCs. It in particular permits the use of P11 which has a higher polarity than P134a. As a practical matter it was in 1988 and is now, highly unlikely that any MDI formulator would set about using any CFC at all in a new formulation There is not much point in getting rid of the P12 if you still use P11.

The compound of higher polarity was often called the 'co-solvent'. It operates to get the surfactant into solution and as a pressure depressant. P11 served those functions in the prior art (as was well known) and would do the same for a claim 1 formulation in which it was used.

It was common ground that nothing turned on the particle size limitation: the size referred to was entirely conventional in suspension MDIs.

Claim 2

"An aerosol formulation as claimed in Claim I in which the compound having a higher polarity than u.c134a is selected from alcohols, saturated hydrocarbons and mixtures thereof."

Claim 5 of 344

It is convenient to mention this here. Claim 1 of 344 is nearly the same in scope as claim 2 of 777. Claim 5 is the only claim of 344 said to have independent validity. It reads:

"An aerosol formulation as claimed in any preceding claim which is free from CFCs."

I am quite unable to see how this claim could have independent validity. Once one has embarked on formulations which are CFC free (which is the whole point of the main claims) leaving CFCs out is utterly self-evident. 1 will say no more about this claim or this patent.

Claim 3

"An aerosol formulation as claimed in Claim 1 in which the compound is selected from ethyl alcohol, iso-propyl alcohol, n-pentane, isopentane, neopentane, isopropyl myristate and mixtures thereof."

Norton's main case concentrated on ethyl alcohol as the co-solvent. They ran other cases (particularly about the use of P134a/P11) too. I was and remain baffled by why they did this. The only co-solvent of interest is ethanol. Freedom to use P11 as a co-solvent is, I would have thought, commercially useless. I propose to consider just the case based on ethanol.

Claim 6

This is dependent on claims 4 or 5. So it is first necessary to summarise claim 4 (itself dependent on claim 1). It requires that the P134a is present by at least 50% by weight and that the weight ratio of P134a: co-solvent is in the range 50:50 to 99:1. Claim 5 narrows the range of P134a (60-95% by weight) and the P134a/co-solvent range to 70:30 to 98:2. Claim 6 then goes on to narrow the claimed range of P134a/co-solvent to 85 15 to 95:5

The precise mathematics do not matter and are slightly complicated because one has to leave regard to the total amount of P134a before considering the P134a/co-solvent ratio. But basically. taking ethanol as the co-solvent, one can see that claim 6 covers the use of just over 5% to something of the order of 15% in the mixture. There is nothing in the patent which teaches why the particular claimed ranges are in any way critical.

Claim 9

This is only independently defended on the basis that Norton's main attacks on the earlier claims fail. Norton have independent attacks based on two specific pieces of prior art. I have been wholly unable to see the point of these independent attacks for reasons I will indicate later. For the present, however, it is sufficient to recite the claim:

"An aerosol formulation as claimed in any preceding Claim in which the medicament is selected from salbutamol, BDP, disodium cromoglycate, pirbuterol, isoprenaline, adrenaline, rimiterol, and ipratropium bromide."

These are the drugs which were at the time dispensed by MDIs, a matter which was well-known.

The Main Attacks

Norton contend that it was obvious to an MDI team in late 1988 to consider formulation of any drug using P134a as the main propellant. The attack has to consider suspension and solution formulations separately, though it is a fair comment that the patent does not proceed on the basis that there is any significant difference between the two sorts of formulation as far as the invention is concerned.

Suspension formulations

So far as suspension forms are concerned, it is said that the skilled man would know that he could use P11 as a co-solvent (as he had done with P12) but would much prefer to use something else because the whole point of reformulation was to do away with CFCs entirely. The self-evident co-solvent was ethanol.

Norton reinforce their case by reliance on open prior disclosures by ICI to each of the major MDI manufacturers in the UK, Glaxo, 3M, Healthcare and Fisons. I heard evidence from Dr Smith, Glaxo's head of formulation at the time, Dr Mills and Miss Monaghan each of ICI. I also received hearsay evidence from ICI's then technical service manger, Mr Kelly, and (from US patent application proceedings) about the ICI disclosure to 3M. By the time of the latter disclosure, 3M's inventors had already had the idea of trying to work with P134a. I am satisfied as a result that.

(1) ICI approached each of these major MDI manufacturers to inform them that they were planning to open factories for the full-scale manufacture of P134a;

(2) In the case of Glaxo the approach was by Mr Kelly and there were two scheduled and at least one unscheduled meeting before the priority date;

(3) ICI specifically suggested the use of P134a for MDIs;

(4) ICI indicated in their view P134a was the only non-CFC propellant which had the desired physical properties and had sufficient toxicity data available to give confidence in the development of MDIs (Dr Smith's Statement. para. 13).

(5) ICI were willing to make available and did make available samples of P134a. The samples were supplied on a non-confidential basis. Because of limited quantities samples were only supplied to potential major users, including Glaxo, 3M and Fisons. Persons in the position of Dr Sciarra could not get their hands even on samples of P134a in 1988.

Each of these matters forms part of the 'state of the art' and is the basis from which the key, Windsurfing, question: was the step from this disclosure to the claim obvious? Later ICI and Glaxo entered into a confidentiality agreement. This was because Glaxo needed to know the details of ICI's P134a manufacturing process. The point was that Glaxo had to work with an utterly reliable material - otherwise they could not get regulatory approval. They needed approval for a formulation with a well-characterised P134a - not any old P134a. I do not think any relevant disclosure was under a seal of confidence, the agreement only being made well after the initial contact between the parties. The significance of the agreement (November 1988) is, if anything. against 3M. It shows that Glaxo firmly thought that P134a was the way forward, otherwise they would not have bothered to go into the agreement at all Likewise (though it is just after the priority date) many other manufacturers clearly so thought: they agreed (by an agreement called IPACT) to pool their knowledge about the toxicocology of P134a 3M were parties to IPACT. There was no suggestion that they, as it were, brought P134a to the party.

Mr Kitchin QC for 3M said it was not shown that all of the above itemised matters formed part of the common general knowledge. I think this must be right, though since they form part of the state of the art by reason of the ICI disclosures 1 do not think this much matters. MDI formulators other than this

significant band of disclosees would not have known of ICI's specific pushing of P134a for MDIs. All they would have known is that P134a was generally being suggested as a replacement for P12 and that it was likely to go into manufacture and so was not thought to be toxic for general purposes. That does not mean, however, that the ordinary formulator would have rejected P134a. On the contrary there was enough known about it for it to command attention for possible use in MDIs. Several other possible propellants may have commanded similar, though rather less attention. Of those suggested, some had problems of flammability others possible long term environmental problems due to release of chlorine.

I think it fair to conclude that P134a was not only known to the ordinary skilled man from his reading, but that he would want to try it as a propellant for MDIs if he could get his hands on it. I do not think he would simply reject it as 'insufficiently characterised' as Mr Kitchin suggested. There is some confirmation for this view in that Dr Sciarra did experiments with P134a when he eventually got some. Though this was after the priority date of the patent (probably in about 1990 or so) he did this without knowledge of the patent and there seems to be no particular advance in knowledge which made that course the sensible thing to do in 1990 but not in 1988. In this regard I pay rather more attention to what Dr Sciarra did, than his hindsight opinion that in 1988 it would not have been obvious to try to reformulate MDIs using P134a. I think that if ICI had offered P134a to him for use in MDIs he would not have rejected the offer - he would have had a go.

I must also say something about the 'toxicity fear'. In December 1987, following the Montreal Protocol. the general propellant/refrigerant manufacturers set up an organisation called PAFT to test the general toxicity of P123 and P134a; This had not yet reported by the priority date. Mr Kitchin suggested that without such clearance the MDI formulator would not be particularly interested in P134a. There are several answers to that. First the patent itself provides no help whatsoever in relation to toxicity. If a man was worried about this before the patent, the patent would do nothing to relieve his anxiety. Second, however, ICI had done some preliminary work on toxicity and indicated that there were no apparent problems to Glaxo and the others. And I think it was pretty self-evident that general problems were unlikely - otherwise ICI (and others) would not be committing themselves to full scale manufacture. There is nothing in the toxicity point.

The principal defence of 3M is that even if the skilled team had considered P134a in 1988, they would have rejected its use. This is because it was known to be a very bad solvent. This in principle is no bad thing for suspension formulations because you do not want the drug to dissolve. But, it is suggested, the skilled man would have been put off because he would know he needed some solubilised surfactant. This is a particularly poor point so far as claim 1 is concerned - it covers the use of P11 which was well established as a co-solvent for just that purpose.

3M suggest that the position was different as far as ethanol is concerned. They say the skilled mall would fear to use this because it might dissolve the drug too much - leading to a potential for Ostwald ripening. Again there is nothing in the patent about this: you cannot tell whether over a period of time this would occur with a particular drug. Moreover the skilled man would know that you do not get this phenomenon in relation to the use of P11 at least with a number of drugs. So, if he uses a small amount of ethanol instead he may well

not find an Ostwald problem. The evidence shows that in relation to this sort of detail the art is empirical. I think there was every reason for the skilled man to pick ethanol as a co-solvent for experimental work with P134a. It was the only potential non-CFC co-solvent which had regulatory approval. Whether or not substantial long-term testing would throw up problems would not be enough to deter him. It was not enough to deter 3M (who took the patent out without knowing whether there would be such problems) and it was not enough to deter Glaxo.

What happened at Glaxo is, to my mind, confirmation of what was obvious. At a very early state after ICI had proposed P134a Dr Smith suggested the use of ethanol as a co-solvent for formulations of two particular drugs. the principal propellant being P134a. Glaxo worked on this for some time before discontinuing for confidential reasons which Dr Smith indicated in camera. They independently came within claims 1 2 and 3 of 777 (and claim 5 of 344). They did not think what they were doing was patentable. As regards claim 6 it is more than likely that they were within this too, though Dr Smith could not be sure. I do not actually think it matters - the claimed ranges are fairly arbitrary. All one can say with confidence is that the skilled team would only use as much ethanol as was necessary. Dr Sciarra suggested that if you used too little ethanol you would not get enough of a pressure drop. And if you put in more you would increase the Ostwald danger. That is in a sense all true - you would not find out with a particular drug until you tried - and the patent would provide no assistance at all. Dr Sciarra's evidence of a potential problem is. I think, undermined by the fact that when he did try using P134a for an MDI he did use ethanol as a co-solvent. Mr Kitchin pointed out that the reason for such use was not made explicit. He suggested that that it was not for dissolving the surfactants, but it is difficult to conceive of any other purpose - and whatever the purpose the ready use of ethanol is hardly consistent with a real fear that it would dissolve the drug enough to create a real Ostwald problem.

This last point is important. From time to time Mr Kitchin would place an imponderable before me and urge that one could not predict 'success'. That all depends on what you mean by 'success'. All the patent specifically discloses is some formulations of some drugs. It provides no information upon which the skilled man can say: 'here is a marketable product.' He is told the product is 'stable' but that is no-where near enough even for him to be sure that Ostwald ripening does not occur over a period of time. 'Success' in terms of the patent means a formulation with P134a and ethanol, even if does not have long-term stability or has long-term toxicity.

Solution Formulations

Mr Kitchin's defence here was essentially that no-one in the late 1980's would be interested in solution formulations - they were yesterday's technology. Hence no-one would try to make a solution formulation. This is an inherently bad point, confusing as it does what a man would want to try for the market as opposed to what is technically obvious. As I have said solution formulations were part of the common general knowledge and a skilled man was entitled to make one even if he did not particularly want to. Given that P134a had physical characteristics similar to P 12 but bad solubilising power and you did not want to use P11 to reduce pressure you were virtually driven to dissolve the drug in something else. The prime candidate for this was ethanol. As to the use of surfactant, that was routine - both for stabilising the solution and lubricating

the valve.

I have come to the clear conclusion that all the claims independently relied upon are obvious and that the patents are bad. I should, however, deal with a number of points made by Mr Kitchin to suggest non-obviousness.

Other work by Glaxo

Glaxo in due course took out several patents on MDIs using P134a. The patents covered things different from that claimed by 3M. The things claimed were, for example, other surfactants which might dissolve in P134a and surfactant coated drugs. I do not think this suggests non-obviousness at all. For all I know these other ideas are inventive and are useful. The point was largely destroyed once it emerged clearly that Glaxo had also done what is claimed by 3M. I say 'once it emerged' because this only was made clear when I permitted Dr Smith to be recalled during Mr Kitchin's closing speech. I did so because I did not want the case to go off on an ambiguity and I could see no injustice in permitting such recall. Amazingly Dr Smith's witness statement was not clear on the point, though one would have thought it self-evidently of great importance to Norton's case if Glaxo had not come within the claim after all the hints from ICI that might well have been evidence of non-obviousness

Work by Fisons

Much the same point as is made upon the Glaxo patent applications is made about some Fisons applications. It is not a fair inference from the fact that Fisons thought some other ideas patentable that they did not consider what 3M claim obvious

The Kelly memorandum

This was an internal memorandum of ICI prepared by Mr Kelly. The version provided came off a computer. Some parts must have been written after October 1988 (probably shortly after) but other parts may have originally been written earlier: some 1986 CFC use figures were given whereas by late 1988 later figures were available. The document is entitled 'Opportunities for Alternatives to CFCs in the Aerosol Sector'. It deals with 'Medical Products' as a separate heading. These would include MDIs as well as topical sprays. It notes the requirement for very low toxicity. It notes a requirement for non-flammability. It says:

"Whilst the current products on the market are all powder suspensions, it has been suggested that if the drug and surfactants were completely soluble in the propellant, this would be equally acceptable. Otherwise the requirement is for very low solubility of the drug in the propellant but sufficient solubility power to incorporate the surfactant."

No-one knows where Mr Kelly got his information from. He was wrong about all current products on the market being suspensions - at least 5 were solutions. Later he said:

"The vapour pressure of 134a and 134 is possibly a little on the high side but indications from discussion with the UK manufacturers of inhalant products suggest that this could probably be accommodated. Poor solubility is likely to be the major drawback requiring development/approval of new surfactants."

Mr Kitchin fastened onto this. Here. he said, is the perception of the industry as recorded by Mr Kelly. The perception was that P134a could only be used once a soluble surfactant had not only been devised but had got regulatory approval.

Now Mr Kelly was not an MDI expert - he was really a technical salesman. Nor is it known to whom he talked when he wrote this passage. though he does record that samples of P134a had been supplied to Glaxo, 3M and Fisons. Certainly he cannot have got this information from Glaxo. It is not even known when the passage was written. He was wrong about solutions. And he did not know that P11 was being used not only to reduce pressure but as a solvent for surfactants I cannot take this document as accurately recording the perception of the industry.

The Boehringer Ingelheim paper

In June 1991, a year after the 3M 777 patent was published (13.6.90) a paper was published by workers at the large drug company, Boehringer Ingelheim ('BI'). It discusses the use of P134a and another possible propellant P227 in MDIs. It contains the following passage:

"Suspension MDIs usually contain a suspending agent to keep the drug particles dispersed, while solution MDIs usually contain a co-solvent agent that is required to fully dissolve the drug species in the liquid propellant vehicle. Hence, it is necessary that the suspending agents and co-solvents exhibit compatibility with P134a and P227. Whereas ethanol is highly miscible with these propellants, the suspending agents (i.e. [the 3 surfactants]) that have typically been used in CFC-containing MDI products exhibit considerably lower solubilities in P134a and P227 than in the CFC blends that are used in current products. In this regard, formulating with these suspending agents, that are well characterised in terms of inhalation safety, will require using much lower levels than have been employed previously in CFC-containing MDIs."

Mr Kitchin submitted that here were BI, 3 years after the priority date, with both ethanol and P134a under their noses, unable to see that ethanol could be used as a solvent for the surfactants. I do not think this is a necessary inference at all. First it is highly likely that BI actually knew about the 3M patent - drug companies notoriously watch each others patents with vigilance Second they were concerned with long term stability, not the sort of thing shown in the 3M Patents. This is shown by the immediately following passage:

"It is uncertain how the lower levels of surfactants will affect the physical stability of reformulated dispersions. Even more unsettling is the fact that physical stability cannot be easily extrapolated from accelerated stability studies, and hence physical instability will not be identified in a particular formulation until the suspension fails."

They may have rejected what 3M taught for their drugs Thirdly the article puts up all sorts of difficulties (eg. possible incompatibility of P134a with existing valve elastomers) and may have been another article written partly with the motive of buying time. Fourthly the article may have wanted to avoid showing interest in any formulation falling within the 3M patents.

None of these points carry the same weight as the direct evidence of what happened when a drug company (3M, Glaxo) and a skilled man (Dr Sciarra) did when

they were presented with P134a. I think 3M have done no more than attempt to appropriate for themselves P134a for MDIs in a self-evident manner. Their patent tells the skilled man no more than would be readily apparent to him given the ICI disclosures.

Attacks based on obviousness over specific prior publications.

The Amended Particulars of Objections, in addition to the disclosures to Glaxo, 3M and Fisons, cite no less than about 17 distinct prior publications over each of which the inventions of 777 and 344 are said to be obvious. This is a bizarre way of going about an obviousness attack. Normally the more the citations the less the invention is likely to be obvious. Those attacking patents should consider carefully each proposed citation before relying on it. Otherwise cases simply become overloaded. A similar point applies to patentees who feel the need to defend as independently valid a mass of subsidiary claims.

In the end Mr Thorley relied upon just two of the citations - though others he contended were part of the common general knowledge. I must consider the two citations separately, though I believe that doing so is pointless commercially. The reason that is so is because it is conceded that the attacks do not reach claim 9 which covers the drugs for which MDIs are used or any new drug for which an MDI formulation might be used in the future. The attacks, if successful, give commercial freedom to do that which no-one is likely to want to do.

Spremunan

The Dictionnaire Vidal of 1979 indicates that a company called Eutherapie was marketing all aerosol vaccine in the 1970s under the trade mark 'Spremunan'. The recipe is given. It consists of a variety of vaccines, a surfactant, '100%, pure alcohol' and P12. No-one knew much about Spremunan. It has not been on the UK market and it is probably not on the market at all. It is not a product of commercial interest. Norton suggest it was technically obvious that that recipe could be modified by substituting P134a for the P12. The argument is highly artificial on any basis. For if there was no particular incentive to make this obscure product at all, there could be no incentive to modify it either. But things can be technically obvious even if of no commercial point and that is said to be the case here. However, if, contrary to Norton's main case and my main finding, P134a was not the or a prime candidate to replace P12 then I cannot see that a case of obviousness is made out. Why, even technically, should one consider using a non or minor replacement P12 candidate for this recipe? If, on the other hand as I think was the case, P134a was a prime candidate, then I think it was technically obvious that it could be used with any inhalation drug and so with this bizarre Spremunan cocktail too.

I should mention an intermediate position discussed in argument: that P134a was sufficiently part of the common general knowledge to be known as a potential replacement for P12 but not that the use of ethanol as a co-solvent was obvious. The argument is then that the non-obviousness of ethanol does not matter because Spremunan supplies the alcohol for his cocktail in any event. But, if ethanol was not obvious, this was for the reasons advanced by Mr Kitchin: that the skilled man would consider it but reject it. I can see no reason why the skilled man would think it worked with the Spremunan cocktail as disclosed. So he would reject it anyway.

In the result the case under Spremunan succeeds, but only because the main

case succeeds too. I do not think it was a useful exercise to plead it.

Abbott EP Application No. 0275404

The case in respect of this is much the same as Spremunan. An example is of a drug called LHRH. It is in suspension and the remainder of the formulation uses P12 as propellant, an optional surfactant and a solvent said to be 'P11 and or Absolute alcohol'. Here, say Norton, one would modify the recipe so as to use P134a instead. But again one would only do so if one had some confidence that alcohol would not cause trouble. If one had the fears for which Mr Kitchin contends one would not have much confidence in the Abbott example. Again the case on this succeeds only because the main case succeeds.

Patent No. 298

This has a later priority date - 18.10.90. Its main claim is for:

"An aerosol formulation comprising a therapeutically effective amount of BDP, a propellant comprising a hydrofluorocarobon selected from the group consisting of P134a, P227 or a mixture thereof, and ethanol in an amount sufficient to solubilise the BDP in the propellant, the formulation being further characterised in that substantially all of the BDP is dissolved in the formulation and that the formulation contains no more than 0.0005% by weight of any surfactant."

In short this is for an ethanol solution formulation of BDP in which no surfactant is used. The subsidiary claims defended independently are claims 4 (2-12% ethanol), 7 (P134a alone) and 8 (P227 alone). The minor amendment sought relates to claim 13 which is not defended separately.

The body of the specification asserts that:

"certain of the preferred formulations of the invention exhibit very desirable chemical stability and provide respirable fractions significantly greater than commercially available BDP products."

The exmples do not (live details of other than some accelerated stability tests. These would not he good enough for regulatory approval (cf. what BI had to say about such tests). Some detail of a respirable fraction is given, but it is not comparative and I heard little about this promise of the patent.

The A version of 777

The principal citation is the A (ie. as filed) version of the 777 patent, published on 30.6.90, a few months before the priority date. Both anticipation and obviousness are relied upon. Anticipation would only cover a small part of the claim and Mr Thorley frankly admitted that the point was of more interest to practitioners than it was commercially.

Mr Thorley acidly observed that 777 covered a solution formulation of BDP which used surfactant this is for leaving it out. I do not see that as in itself destructive of the patent. There can be invention in leaving out that which everyone thought was necessary. I must consider this patent on the basis of the cited art and common general knowledge. I begin with anticipation, a lack of

novelty.

777A says of its formulations (p 5, 8-11):

"The surface active agents are generally present in amounts not exceeding 5% by weight of the total formulation. They will usually be present in the weight ratio 1:100 to 10:1 surface active agent:drug(s), but the surface active agent may exceed this weight ratio in cases where the drug concentration in the formulation is very low." (Range A)

A little later it says (p.5, 51-52):

"The concentration of medicament depends on the desired dosage but is generally in the range 0.01 to 5% by weight." (Range B)

And 777A also discloses the use of BDP, ethanol and P134a in several places.

So, say Norton if you use BDP with a combination of 0.01% of drug (bottom of Range B) with a surfactant/drug ratio of 1:100 (minimum amount of surfactant from Range A) you get 0.00001% of surfactant in the mixture. This is less than the maximum called for by claim 1 and so there is anticipation.

For a prior teaching to be novelty-destroying one must find clear and unmistakable directions in the earlier document to do something within the claim. There may be cases where a patent teaches any point on a plane defined by two ranges, or indeed, a point in n-dimensional space where the prior teaching provides for n ranges. It may do so explicitly or by necessary implication. The prior document is to be read through the eyes of the skilled man, a point of particular importance if one is considering implication. Here there is no explicit teaching so the question is whether the skilled man is taught by necessary implication. I do not think he is. He would read 777A sensibly. He would see that if you only have a very low amount of drug (0.01%) you may need more surfactant in ratio, but not absolute terms. The surfactant is there to do a job. You have to have enough, whatever that may be. The skilled man would not say: 'this specifically teaches me that if I have a very low proportion of drug I must use very little surfactant.' I think the anticipation case fails.

I turn to obviousness over 777A. 777A has 3 examples of a solution formulation of BDP, examples 10-12. The recipes are the same for all 3 except for the surfactant. One of each of the 3 surfactants is used in each example in the same amount. Norton's case is very simple: the skilled mall would always try simple experiments to see what the effect of various levels of surfactant were. He would be aiming to use the minimum quantity necessary. One would see how much was necessary - if none was then none would be used. I think the evidence bears this case out. Dr Smith said he would, on seeing the examples, question the need for the surfactant altogether (pp.265-7) - it served no obvious purpose in a solution. Dr Sciarra, was asked about the Abbott patent:

"Q. Would you use a surfactant such as sorbitan monooleate?

A. According to the teachings of this particular patent, and in this combination, it indicates that it is needed. Based on prior experience with solutions, I am not sure whether I would need it or not. I would probably . . . I should not say probably. I would try it maybe with and without.

Q. You would see what happens.

A. Yes."

It was not suggested that his reaction here was atypical. I think the skilled man would react in the same way to the examples of 777A. Moreover there is this to be considered: that Dr Sciarra would not as a matter of course on general principles put a surfactant in a solution formulation (p.584, 1-3). I do not think it was inventive to leave out the surfactant of the examples.

The defence to obviousness echoes the defence to obviousness of a solution formulation formulation of 777A: that the skilled man would not be interested in solutions at all and hence would have no interest or motive to leave out the surfactant (or indeed, put it in). That seems to be to confusing what the skilled man would actually wish to do with that which was technically self-evident to him.

It is also suggested that the skilled man would have understood from 777A that a surfactant was necessary. All the specification says (speaking of its formulations generally, including suspension formulations) is:

"The aerosol formulation comprise a surface active agent to stabilise the formulation and lubricate the valve components." (p.2.15-16.)

This is hardly a teaching that the surfactant is essential in all solution formulations. Dr Sciarra suggested in his witness statement:

"In the light of what is said in 777A, he [i.e. the skilled man] would have been concerned that removing the surfactant, or significantly reducing its concentration, would adversely affect one or more of these properties of the formulation. He would have understood from statements in 777A that the authors of that document had found surfactant to be a necessary component of the BDP/P134a formulation; and the fact that surfactant had been included would have suggested to him that it was necessary, because as I have said, formulators do not include unnecessary components."

I find this difficult to reconcile with what Dr Sciarra said about the Abbott specification. 777A simply does not teach that surfactant is necessary for a solution and it is going too far to say it teaches this by implication.

In reaching this conclusion I pay no attention to the experts on toxicology who were called by each side, Professors Caldwell and Florence. Neither were MDI specialists and I did not think their evidence assisted.

I turn to claim 4 which calls for 2-12% ethanol. The examples of 777A use about 25%. It is said that it was unprecedented for a solution formulation to use less than this, ergo so to do is non-obvious I do not agree. It is accepted that formulation is empirical. You would want to use enough ethanol to dissolve the BDP and to adjust the pressure, If the amount was within claim 4 for the dosage required, then that is what you would do.

I defer consideration of claim 8 for the present and turn to the other citation.

Gunella

This appears to be a document in Italian published in something called 'Minerva Pneumologica'. No admission was specifically sought or given, though it was in relation to other citations. Somewhat typically of the way this case was got together, Norton then failed to prove publication properly. Judging by the date on the original printed version, however, on balance I think publication is proved - in 1975.

The document relates to a product called 'Terapia'. It discloses a BDP solution with CFC propellants and no surfactant. It is said to be technically obvious to modify this by using P134a. However the product described is so odd - for instance it contains a propellant 113 which Dr Sciarra a doubted was approved, that I doubt anyone would have taken the disclosure seriously. Dr Sciarra said he had no idea what would happen if P134a were used instead of the stated propellants. One could find out, no doubt, but with what result Dr Sciarra was not prepared to say. I do not think the case on Terapia is made out. Moreover I think this is another example of the case being overloaded by material which self-evidently was not Norton's best case.

Claim 8

This is for a surfactantless BDP solution in ethanol using P227 as a propellant. It is common ground that in May 1990 Hoechst gave a presentation to the IPAC steering committee in which Hoechst indicated that, like P134a, P227 was nonflammable, possessed a suitable vapour pressure and had an ozone depletion potential of 0. It was also disclosed that the compound had exhibited minimal toxicity in preliminary studies. The disclosure was to a number of major companies concerned with MDIs. These consisted of or included Boehringer Ingelheim, Ciba Geigy, Fisons, Merck, Rorer, Schering, and, notably, 3M. 3M clearly fastened onto this and included P227 in this patent as a possible propellant. There is an example in the patent, but all it says is that an MDI was made using P227. No information of any kind is given about how it worked, stability or anything like that.

3M say it is not shown that by the relevant date (October 1990) P227 was common general knowledge - part of the background knowledge of the ordinary skilled man. And it is true that neither Glaxo (who were not members of IPAC at the time) nor Dr Sciarra knew at that time about P227. It follows, say 3M, that one cannot 'mosaic' knowledge of P227 with some other piece of prior art which is not common general knowledge. In particular one cannot say that the ordinary skilled man, reading the 777A application, would bring to bear any knowledge of P227. So he would not say to himself: 'This proposes P134a. I know that P227 is an alternative to P134a and so anything which I could do with P134a I could equally do with P227.'

This argument fails. It is true I cannot find that P227 was part of the knowledge of any ordinary skilled man when neither Glaxo nor Dr Sciarra had heard of it. But there would be something wrong in 3M (or anyone else) being able to take for themselves Hoechst's disclosure simply because that was not made more widely known. The disclosure told all those who heard it that P227 could, in principle, be used in any MDI. No ordinary citizen would regard using that information for any particular MDI as inventive, as deserving a monopoly. But the question is why not?

I think the reason is this: 777A makes obvious the use of a solution formulation of BDP as I have indicated. It uses P134a as the propellant - a propellant which itself was common general knowledge by 1990 on any view. The skilled man would, however, also appreciate that any equivalent of P 134a would serve as well. So 777A also made obvious a solution formulation of BDP using any equivalent of P134a. P227 is no more than a member of the set of such equivalents. As such its use (and that of any other, even future, equivalent) is obvious.

In the result I hold that all three patents are invalid for obviousness and must be revoked. I am not sorry so to do: I do not think 3M provided mankind with any advance in knowledge by any of the disclosures in the patents. In so holding I am conscious I am differing in the result from that of the Opposition Division of the EPO. Unlike them, however, I have had the advantage of learning about ICI's specific disclosures and of Glaxo's reaction to those disclosures.

DISPOSITION:

Judgment for the Petitioner.

SOLICITORS:

Linklaters & Paines; Roiter Zucker